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TITLE: Immune Surveillance, Cytokines and Breast Cancer Risk:
Genetic and Psychological Influences in African American
Women

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13. ABSTRACT (Maximum 200 Words) Breast cancer cells are known to bear determinants that would allow tumor specific immune responses. However, initiation and amplification of such immune responses are critically dependent upon the balance in TH1 and TH2 cytokine profiles. This molecular epidemiological study evaluates the impact that variability in cytokine profiles, (inferred from functional polymorphisms in cytokine genes), may have on breast cancer risk among urban African-American women. In the first phase of the study, DNA collected and approved for additional study as part of a previously funded Case-Control investigation (n=1600) will be assessed for cytokine polymorphisms. Because cytokine profiles are also known to be affected by environmental factors, particularly levels of stress, this study also evaluates the relative contribution of genotype and stress influences using data collected for that purpose from a sub-sample of healthy Controls (n=400) recruited from the "graduates" of the larger study. Results will allow evaluation of the possibility that deficits in cytokine responses due to genetic or environmental factors may contribute to breast cancer risk. Based on these findings, women at risk for breast cancer because of polymorphisms in genes important to effective immune surveillance could be targeted for innovative prevention strategies including stress reduction and immune modulators.				
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Title: "Immune surveillance, cytokines and breast cancer risk: Genetic and psychological influences in African American women"

Principal Investigator: Dr. Dana H. Bovbjerg

INTRODUCTION:

The study supported by this IDEA grant award is designed to provide the first critical test of the hypothesis that dysregulation of cytokine production profiles necessary for effective immune surveillance against transformed cells may contribute to increased risk of breast cancer. More specifically, we hypothesize that women whose cytokine responses tend to favor humoral (Type 2) over cell-mediated (Type 1) responses are at risk for developing breast cancer. Because assessments of cytokine responses in blood samples from patients are likely to be affected by the presence of clinical disease and its treatment, we will test this hypothesis using a molecular epidemiologic approach. In the context of a previously funded case-control study (n=1600), we will evaluate the role of polymorphisms in cytokine genes associated with dysregulation in relation to breast cancer risk. We will also explore the relative contribution of genotype (cytokine polymorphisms) and environmental influences (e.g., stress-induced immune modulation) to cytokine responses in a sub-sample of healthy control subjects (n=400).

The proposed research "piggy-backs" on a project (Ambrosone, PI) recently approved for funding as part of a Behavioral Center of Excellence award from the Army (DAMD-17-01-1-0334, Bovbjerg, PI). In the "parent" project, African-American women with breast cancer will be ascertained from hospitals in NYC that have the largest referral patterns for African-Americans in Manhattan, Bronx, Brooklyn and Queens. Through collaborations with physicians at each of the participating hospitals, newly diagnosed breast cancer patients will be identified for rapid case ascertainment. Age-matched controls will be selected using Random Digit Dialing (RDD). Upon agreement to participate in the study, interviews will be conducted (n=1600) and a blood specimen drawn for DNA extraction. For the proposed study, appropriate banked DNA will be genotyped for the cytokine polymorphisms of interest. Additional newly obtained blood specimens from consenting Control participants (n=400) will be processed for cytokine responses (phenotype), and an additional set of questionnaires focused on psychological stress will be completed. Data analyses will be conducted using standard approaches.

This study represents an innovative combination of behavioral research and molecular epidemiology, synthesizing concepts from both disciplines to address critical questions regarding breast cancer etiology. By exploring hypotheses related to psychoneuroimmunology and using technology and paradigms from molecular epidemiology, this research may make important contributions to identifying causes of breast cancer so that it may be eradicated. The study is economical and efficient, in that it builds upon an already-funded case-control study of breast cancer. The infrastructure is already in place for all aspects of this study. Of course, the aims of the study are somewhat speculative, but are grounded in a substantial body of previous literature on the role of cytokines in other diseases and the effects of stress on cytokine responses. By examining case-control differences in cytokine polymorphisms, the role of this aspect of immune function in breast cancer may be elucidated. Furthermore, the evaluation of stress effects on cytokine responses in vitro, particularly in relation to genotype, may suggest a mechanism and provide stronger support for a possible role of stress in breast cancer etiology.

BODY:

We have yet to receive notification of HSRRB approval through the USAMRAA office (Human Subjects Protection Scientist, Dr. Maryann Pranulis) for this Project. We have also yet to receive approval for the "parent" project, DAMD-17-01-1-0334, (Human Subjects Protection Scientist, Dr. Maryann Pranulis), which will be the entry point for recruitment for participants in this study. We have therefore fallen substantially behind our anticipated timeline for completion of the tasks listed in the Statement of Work. Although we have submitted all required and all requested modifications and additional materials in a timely fashion, we have received no indication from Dr. Pranulis that this material has as yet been formally reviewed by the HSRRB. Indeed, according to our records, our last contact with Dr. Pranulis about the review of these materials was in April of this year when we sent her the revisions to the consent and protocol she had requested.

Given our experience of the lengthy review process, we therefore propose to modify our original Statement of Work, to include as a new Task (Months 0-18): Successful application for HSRRB approval through the USAMRAA office. Given the 2-10 month time period required for turn around of similar materials by the HSRRB of the USAMRAA after previous submissions for other funded projects of ours that have been submitted to Dr. Pranulis, we anticipate approval by 2004.

As allowable in the absence of approval by the HSRRB of the USAMRAA, we have focused our energies on completion of required local Institutional Review Board requirements (approved by Mount Sinai School of Medicine 5/8/02), as well as Task 1: Setting up of study procedures of our funded Project. We have trained research assistants and confirmed reliability; we have produced study questionnaires; we have established procedures for coordination with the "parent" project; we have established procedures for coordination with the Recruitment, Tracking, and Interviewing Core of the "parent" Behavioral Center of Excellence (Bovbjerg, PI). This groundwork should enable us to move quickly to the next Tasks, as soon as approval from HSRRB is obtained. As we have husbanded our resources, we anticipate being able to address all proposed Tasks in a timely manner after approval by the HSRRB of the USAMRAA. Recognizing the late start date, and an anticipated request of a no-cost extension of the Center and this project, we propose to modify the timeline of program of work to delay the start date for Tasks 2-7 by 16 months and the end dates by 12 months. For the additional 6 months delay anticipated, we plan to "make up for lost time" through enhanced recruitment efforts, and greater efficiencies in conducting the proposed research.

KEY RESEARCH ACOMPLISHMENTS:

At this point in the research, with no approval by the HSRRB of the USAMRAA, no results are yet available.

REPORTABLE OUTCOMES:

At this point in the research, with no approval by the HSRRB of the USAMRAA, no reportable outcomes are yet available.

CONCLUSIONS:

At this point in the research, with no approval by the HSRRB of the USAMRAA, no results are yet available. If the results of the proposed research are consistent with study hypotheses, the study could have profound implications for the eradication of breast cancer. The results of the proposed research may suggest new means of evaluating genetic risk of breast cancer in healthy women, as well as novel intervention strategies for long term reduction of that risk, including stress reduction, as well as biological response modifiers designed to ameliorate dysregulation of cytokine profiles.

REFERENCES:

N/A

APPENDICES:

N/A